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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,977	10/02/2003	**Jack Nguyen**	33328.04905.US01/4905	9061

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/677,977	NGUYEN ET AL.
	Examiner	Art Unit
	TERESA WESSENDORF	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9,11-16,45,48,51-53,57-59,61-63 and 65-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, 9, 11-16, 45, 48, 51-53, 57-59, 61-63 and 65-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/13/11 has been entered.

Status of Claims

Claims 1, 3-7, 9, 11-16, 45, 48, 51-53, 57-59, 61-63 and 65-78 are pending and under examination in the application.

Withdrawn Rejection

In view of the amendment to claim 66 the objection has been withdrawn. Also in view of the amendments to the claims the rejections under 35 USC 112, 1st paragraph (new matter and written description) and 35 USC 103 over Guinto are withdrawn.

Information Disclosure Statement

The information disclosure statement filed on 4/13/11 and has been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 51 is objected to because it depends upon cancelled claim 50. Appropriate correction is required.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

Claims 1, 3-7, 9, 11-16, 45, 48, 51-53, 57-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

Claim 1, step (a) with the different amino acid positions being mutated are not supported in the as-filed specification.

Applicants state that support can be found in the specification as originally filed, for example, at page 20, lines 3-7; at page 25, lines 3-16, and at page 28, lines 1-3; and Table 3.

These sections do not support the present claim mutations at the recited specific residue locations. For example, page 20, lines 3-7 does not exist. Page 20 of the as-filed specification (10/2/03) contains only up to line 5. Page 25 and page 28 do not recite mutations of the claim residues at all of the claim positions. Table 3 at page 21 recites only some but not all of the claimed residues. Table 3 does not recite residues 58, 64, 97-98, 100 and 217.

Claim Rejections - 35 USC § 112

Claims 1, 3-7, 9, 11-16, 45, 48, 51-53, 57-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1, 53, 59 and 63 which recite "each member of the library has N mutations relative to a wild-type mammalian protease scaffold or a biologically active portion thereof; and N is a positive integer" are vague and indefinite. The preceding steps or statements do not recite the variable N. Rather only mutations at the specific residues. It is vague and indefinite whether N is different from the mutations at the specified claimed residues. Furthermore, the claim "each different mutein protease in the library is a member of the library" appears redundant. It is suggested deleting the phrase.

2. Claims 1, 53, 59 and 63 step (b) is vague and indefinite as to whether the target is a protein or polypeptide. This is inconsistent with the preamble which recites only protein.

3. Claims 1, 53, 59 and 63 step (b) which recites "the target protein is selected from among" is vague and indefinite as there seems to be no selection that can be made as the members are "among" those recited therein. Also, the claim "among amino acid residues between" is vague and indefinite as to which residues are considered as "between."

4. Claims 1, 53, 59 and 63 step © is vague and indefinite as to the recitation of "substrate sequence". This is lacking from the preceding step and unclear as to its metes and bounds given that the target protein does not recite a sequence.

5. Claims 1, 53, 59 and 63 step d) recitation of "based on the measured activity" is not a positive, manipulative process step.

6. Claims 1, 53, 59 and 63 step (e) is vague and indefinite as there seems to be a lack of nexus of this step with the preceding steps a)-d). It is vague and indefinite as to the steps included an/or precluded in the testing.

7. Claims 1, 53, 59 and 63 step (d) is vague and indefinite as to the aspect that the target protein is **involved** with a disease or pathology. This rejection has the same import to e.g., claim 11.

8. Claims 3-6 are vague and indefinite as to the given N range since the base claim does not recite the location, if any, of the N in the protease mutein.

9. Claim 16 is vague and indefinite as to step (e) given that the mutations are already recited in the base claim.

10. Claim 52 is vague and indefinite as to the "in vivo assay" since the base claim does not recite for "in vivo" testing. The preceding steps do not recite occurrence in vivo. It is vague and indefinite as to the metes and bounds of the in vivo assay.

Claim Rejections - 35 USC § 102/103

Claims 1, 3-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lien et al(Combinatorial Chemistry and High Throughput Screening, 1999)(as evidenced by Shi et al, USP 20020197701) for reasons of record as repeated below (and modified to address the present amendments).

For claims 1, 3-7, 13, 16, 45, 51-53, 57-59, 61 and 67-78, Lien discloses at e.g., pages 73-75 a method of identifying serine proteases using targeted combinatorial mutagenesis of serine proteases with N mutations (e.g., Fig. 1, page 74). The method comprises producing sizeable libraries of mutant enzymes (N mutations), contacting the library with a substrate and identifying the mutant. Screening and selecting methods both depend not only on the activity and specificity of mutant proteins but also on their individual expression levels (e.g., page 77, col. 1, first complete paragraph). Lien discloses at e.g., page 77, first incomplete paragraph, quantitative assessments of cleavage made by monitoring the hydrolysis (inactivation as claim) of a set of synthetic peptides esters in a colorimetric plate assay(testing as claim). Lien discloses at

e.g., page 73 that the mutant enzyme is useful for therapy as in blood coagulation.

Lien discloses at e.g., pages 77-80 mutations of amino acids at positions 215 and 216. Lien discloses that positions 191 and 192 are tolerant to substitutions where small residues are preferred for position 191, his for 213; M190A. Fig. 2 shows the residues targeted for amino acid substitutions such as, 190, 191, 192 and 218 (recited as among the between residues in claim 1).

For claim 13, Lien discloses mutants with improved cleavage of at least 62.

For Claim 56, Lien discloses that phage displayed proteins can be subjected to in vitro selection procedures, e.g., page 77, first incomplete paragraph, col. 1.

For claims 16, 45, 57, Lien discloses at e.g., page 74, chemical mutagenesis, passage through bacterial mutator strains and PCR. (See also e.g., paragraph bridging pages 76-77.)

For claim 52 Lien discloses at e.g., page 76, col. 2 "in vivo" selection.

For claim 61, Lien discloses at e.g., page 86, col. 2, first incomplete paragraph, granzyme B.

For claims 69, 72, 75 and 78, Lien et al discloses at e.g., page 76, col. 2, and last incomplete paragraph chromogenic substrates.

For claims 68, 71, 74 and 77 Lien discloses at e.g., page 78, col. 1-col.2, under Screening Methods, tetrapeptide with P1=Phe.

The claim inactivation of a target protein involved with a disease or pathology in a mammal that ameliorate a disease is a property inherent or implicit to the method of Lien et al which uses the same compound in the method. [This is evident from the teachings of Shi et al at e.g., paragraph [0003]. Shi states that members of the serine **protease** family which play important roles in a range of cellular functions and which have demonstrated causative roles in human **diseases** include tissue-type plasminogen activator and thrombin (thrombosis and blood clotting), urokinase-type plasminogen activator (cancer and metastasis), trypsin and elastase (emphysema and liver **disease**) and angiotensin converting **enzyme** (hypertension).

Response to Arguments

Applicant submits that growth hormone is not recited as a target protein in claim 63, and hence Lien et al. cannot anticipate claim 63 for this reason.

In reply, a reference is evaluated in its entirety rather than by their specific disclosures. Growth hormone is but one of the many target proteins taught by Lien. Lien teaches other target proteins at e.g., page 87, col. 1; such as antibodies and epidermal growth factor at e.g., page 88 and further cites or refers to numerous publications regarding the different substrate specificity of the different proteases.

Furthermore, that the claim target protein is involved in different diseases or pathologies would be inherently accomplished by the methods of Lien since the same process steps comprising the same compounds is taught by Lien (as evidenced by Shi).

Lien teaches at e.g., page 73, col. 1:

> "…{i}t is useful to be able to generate proteases with new and desirable cleavage specificities. Such enzymes….. could have practical applications in biotechnology…. therapy (modulation of zymogen cascades, such as blood coagulation)….

Shi et al. teaches at e.g., paragraph [003]:

> Members of the serine protease family which play important roles in a range of cellular functions and which have demonstrated causative roles in human diseases include tissue- type plasminogen activator and thrombin (thrombosis and blood clotting), urokinase-type plasminogen activator (cancer and metastasis), trypsin and elastase (emphysema and liver disease) and angiotensin converting enzyme (hypertension).

As applicants stated at page 27 of the previous REMARKS, claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. Rosemount lnc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983).

So read, the specification at e.g., page 52, lines 1 recite a caspase, as the specific target protein (see also claim 12). Thus, the unstructured protease can also cleave another protease(s) which is the target protein.

[The target protein taught by Shi is the same target protein as claimed that are involved in the different diseases. Please note that the diseases taught by Shi are the same diseases as listed at e.g., Table 1, page 12 of the instant specification].

Claim Rejections - 35 USC § 103

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lien et al in view of either Harris et al (The Journal of Biological Chemistry)(I) or (Current Opinion in

Chemical Biology(II) and Waugh et al (Nature Structure Biology) for reasons of record as reiterated below.

Lien is discussed supra. Lien does not disclose the enzyme as granzyme (albeit suggests said granzyme, above) and the substrate as caspase (elected species).

Harris et al discloses at page 27364, identification of in vivo targets of granzyme B based on the elucidation of the substrate specificity of granzyme B. For example, Harris et al. teaches that based on the substrate specificity of granzyme B, certain caspases (caspases 3 and 7), based on their sequences, are more likely substrates then other caspases. Harris et al., also teaches that based on the sequence specificity of granzyme B, nuclear lamin A and nuclear poly(ADP)ribose polymerase (PARP) are potential in vivo substrates for granzyme B. Harris et al. I also teaches that amino acid position Arginine 192 is a structural determinant of specificity of granzyme B, since granzyme B mutations R192E and R192A exhibit reduced hydrolysis of the optimal tetrapeptide substrate Ac-IEPD-AMC and non-optimal tetrapeptide substrate Ac-IKPD-AMC compared to the wild-type enzyme. Harris also discloses at e.g., pages 27372 up to and 27373:

> ….{T]here is a functional relationship between the preferential substrate sequence of granzyme B and the activation site of members of the caspases (Fig. 5D).

> Indeed, studies have shown that granzyme B cleaves and activates several **caspases involved in apoptosis.** Our data on the substrate specificity of granzyme B suggest that caspase 3 and caspase 7 are preferentially activated during apoptosis. Knowledge of the extended substrate specificity of granzyme B allows for the proposal of additional targets of granzyme B during apoptosis. The substrate specificity of caspase 6 matches that of granzyme B, suggesting that both enzymes cleave the same substrates. Several proteins known to be cleaved during apoptosis, such as nuclear lamin A….
> The identification of their specificity will further expand our knowledge of the role that granzymes play in **cytotoxic, lymphocyte-mediated cell death.**

Harris (II) throughout the article, at e.g., pages 127-129, basically discloses the same method as Harris (I).

Waugh discloses at page 762 that granzymes are a vital component of the cytotoxic lymphocyte's ability to induce apoptosis, contributing to rapid cell death of a tumor or virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use as the serine protease granzyme in the method of Lien. Harris teaches that granzyme is a substrate for caspases or caspases can act as substrate depending on its sequence. Accordingly, one would have a reasonable expectation of success in using other serine protease, such as granzyme as taught by Lien as the other serine proteases. Furthermore, one would also have a reasonable

expectation of success in using granzyme as an enzyme for caspase substrate depending upon the sequence contain in each enzyme as taught by Harris above. One would be motivated to use either caspase or granzyme to act as enzyme or substrate due to the dual role each enzymes exhibits depending upon the sequence that is contained therein. Furthermore, caspase and granzyme are only the two most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid.

Response to Arguments

Applicants state that the Examiner must review the results in the Example as a whole. Picking and choosing only portions of the Example is not representative of the results depicted in the Example. In this case, a complete review of the results in Example 11 exemplifies that the exemplified protease granzyme B mutein I99A/N218A inactivates the activity of caspase by cleavage at an identified inactivation sequence at residues 260-265 (SEQ ID NO:2) (see e.g. at page 52, lines 6-7). In contrast to cleavage of the activation sequence that is set forth in SEQ ID NO:4, which is the normal sequence cleaved by wild-type granzyme B to activate caspase, cleavage of this inactivation sequence in caspase-3 set forth in SEQ ID NO:2 inactivates an activity of caspase-3. Thus, the Example compares the activity

of wild type granzyme B, (which normally cleaves that activation sequence in caspase-3 set forth in SEQ ID NO:4) and the mutein I99A/N218A for inactivation cleavage and inactivation of an activity of caspase-3. First, Applicant's argument that Harris et al. teaches that granzyme B activates caspase goes to the limitation in the claims of step e) "testing the identified protease(s) or biologically active portion thereof for cleavage and inactivation of an activity of the target protein that contains the substrate sequence, thereby identifying a protease mutein or a biologically active portion thereof that inactivates an activity of a target protein that is involved with the disease The Example states that the mutant granzyme B I99A/N218A is able to cleave caspase-3 at the inactivation sequence as represented by a shift in cleavage product of the appropriate size for the cleaved peptide, while "wild-type granzyme B does not cleave the peptide" (see e.g. at page 52, lines 16-27). The Example further describes that the cleavage of the inactivation sequence results in cleavage of the small subunit of caspase-3 (see e.g. at page 52, line 28 to page 53, line 2). Further, the Example describes that the mutant can cleave and inactivate an activity of full-length caspase-3 as assessed by assaying the activity of caspase-3 for its substrate Ac-DEVD-AMC (see e.g. at page 53, lines 3-7). The results in the Example show that the

mutant granzyme B dramatically inactivates the activity of caspase-3 with a Vmax in the presence of the mutant granzyme B of approximately zero (see e.g. at page 53, lines 7-13). The Example further describes that the mutant granzyme B also inhibits an activity of caspase-3 as assessed in assays assessing apoptosis. While the Example shows that at low concentrates the mutant activates caspase-3 by cleaving the activation sequence, the result states that "at high concentrations it inhibits caspase-3 by cleaving at the inactivation sequence" (see e.g. at page 53, lines 14-24). Finally, the Example demonstrates that the mutant granzyme B can effectively antagonize caspase- induced activation by wild type granzyme B (see e.g. at page 53, line 25 to page 54, line 3). For example, the Example states that "as shown in Figure 7B, the mutant granzyme B antagonized the effect of wild type granzyme B to induce apoptosis by inactivating the caspase-3." Thus, the Examples clearly demonstrates practice of the method as claimed by generating a protease mutant; measuring the cleavage activity and/or substrate specificity for a substrate sequence in a target protein (here, the inactivation cleavage sequence in caspase-3 as set forth in SEQ ID NO:2) and identifying a mutant that has increased cleavage or substrate specificity therefor; and testing the identified mutant for inactivation of an

activity of the target protein (here, the activity of caspase-3 to cleave is substrate Ac-DEVD-AMC or the activity of caspase-3 to induce apoptosis). This is in direct contrast to the findings in Harris et al.

In reply, Harris is not in direct contrast to the Example in the specification, cited above. Rather, concurs with the findings in the Example.

Harris et al. I, in the abstract, states:

> Mutagenesis of arginine 192 to glutamate reversed the preference for negatively charged amino acids at P3 to positively charged amino acids. The preferred substrate sequence matches the activation sites of caspase 3 and caspase 7 and thus is consistent with the role of granzyme B in **activation** of these proteases during apoptosis. [Emphasis added].

Thus Harris teaches mutations of 192 to glutamate activate caspase 7 which is different from the caspase-3 disclosed in the specificiaton that is inactivated by the single mutant granzyme B I99A/N218A. (The claims recite for several mutants). Since there are apparently several caspase, activation and inactivation appear to be sequence dependent, as taught by the reference above.

Therefore, the combined teachings of the prior art is prima facie obvious to one having ordinary skill in the art at the time the invention was made. The claimed method steps are

routine steps in screening and identifying a **specific** mutant from a library of mutants that binds to a **specific** target protein to identify a protease mutant with improved (e.g., increased) property against its target. The claim method is nothing more than a predictable result expected of the method of screening protease muteins against a target protein. KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

Double Patenting

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, for example, of copending Application No. 12/005949 ('949 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim method is similar, if not nearly identical to the method of the '949 application. The subject matter of the instant and the '949 applications overlap in scope.

Response to Arguments

Applicant requests deferral of resolution of this issue. It is not possible to assess whether claims at allowance in each application will overlap requiring a terminal disclaimer until there is an indication of allowable subject matter in at least one application. It is premature to file a terminal disclaimer at this time. If, when one or both applications are deemed allowed, it is determined that a terminal disclaimer is necessary, Applicant will file a terminal disclaimer.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner
Art Unit 1636